Lactulose

TRADE NAMES

Duphalac (Solvay), Chronulac (Aventis), Constilac (Alra), Cephulac (Aventis), Generlac (Morton Grove), Constulose (Alpharma), Enulose (Alpharma), Cholac (Alra), Kristalose (Bertek).

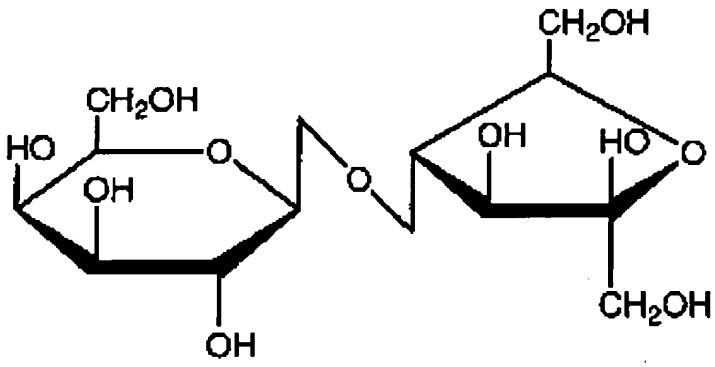
DESCRIPTION

Lactulose is a semisynthetic disaccharide comprised of the sugars D-galactose and D-fructose. It is not found naturally. The sugars are joined by a beta glycosidic linkage making it resistant to hydrolysis by human digestive enzymes. There is no disaccharidase in the microvillus membrane of small intestine enterocytes that can hydrolyze **lactulose**; nor is the disaccharide absorbed from the small intestine. **Lactulose** is, however, fermented by a limited number of colonic bacteria. This can lead to changes in the colonic ecosystem in favor of some bacteria, such as lactobacilli and bifidobacteria, which may confer some health benefits.

Lactulose is used in the treatment of **constipation** and hepatic encephalopathy. The efficacy of **lactulose** in these conditions is based on its fermentation in the colon by certain bacteria and the increase of the biomass of these bacteria in the colon. The products of fermentation are mainly organic acids, such as lactic acid and small-chain fatty acids, which, by exerting a local osmotic effect in the colon, result in increased fecal bulk and stimulation of peristalsis. The higher doses used for hepatic encephalopathy lower the colonic pH, and ammonia, in the form of ammonium ions, is used by the bacteria for amino acid and protein synthesis. This lowers the serum ammonia levels and improves mental function.

The stimulation of the growth of bacteria, such as bifidobacteria, may have other health benefits, such as protection against cancer of the colon. **Lactulose** is referred to as a bifidogenic factor. Substances such as **lactulose** that promote the growth of beneficial bacteria in the colon are called prebiotics. Prebiotics are typically nondigestible oligosaccharides. In addition to its uses in treatment of hepatic encephalopathy and **constipation**, **lactulose** is used in Japan in functional foods and as a nutritional supplement. These uses of **lactulose** are being explored in the United States, as well.

Lactulose is a solid substance that is very soluble in water and has a sweet taste. It is sweeter than lactose but not as sweet as fructose. **Lactulose** is also known as 4-O-beta-D-galactopyranosyl-D-fructofuranose. Its molecular formula is $C_{12}H_{22}O_{11}$, and its molecular weight is 342.30 daltons. The structural formula is:



Lactulose

ACTIONS AND PHARMACOLOGY

ACTIONS

Therapeutically, **lactulose** has laxative and ammonia-detoxifying actions.

Supplemental **lactulose** may have antitumor, antimicrobial, hypolipidemic and hypoglycemic actions in some. It may also help improve mineral absorption and balance, and may have antiosteoporotic activity.

MECHANISM OF ACTION

The possible antitumor activity of **lactulose** might be accounted for, in part, by the possible antitumor action of butyrate. Butyrate, along with other short-chain fatty acids, is produced by bacterial fermentation of **lactulose** in the colon. Some studies suggest that butyrate may induce growth arrest and cell differentiation and may also upregulate apoptosis, three activities that could be significant for possible antitumor activity. **Lactulose** may also aid in increasing the concentrations of calcium and magnesium in the colon. High concentrations of these cations in the colon may help control the rate of cell turnover. High concentrations of calcium in the colon may also lead to the formation of insoluble bile or salts of fatty acids. This might reduce the potential damaging effects of bile or fatty acids on colonocytes.

Lactulose may promote the growth of favorable bacterial populations, such as bifidobacteria, in the colon. Bifidobacteria may inhibit the growth of pathogenic bacteria, such as *Clostridium perfringens* and diarrheogenic *Escherichia coli*.

Lactulose may aid in lowering serum triglycerides in some. The mechanism of this possible effect is unclear. Decreased hepatocyte *de novo* synthesis of triglycerides is one hypothetical possibility. **Lactulose** may also lower total cholesterol and LDL-cholesterol levels in some. Again, the mechanism of this possible effect is unclear. Propionate, a product of **lactulose** fermentation in the colon, may inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.

The possible effects of **lactulose** on blood glucose may be explained in a few ways. **Lactulose** may delay gastric emptying and/or shorten small-intestinal tract transit time. This may be via the short-chain fatty acids produced from **lactulose** in the colon. Short-chain fatty acids may be involved in the so-called "ileocolonic brake," which refers to the inhibition of gastric emptying by nutrients reaching the ileo-colonic junction. Short-chain fatty acids may also stimulate contractions of the ileum and shorten ileal emptying. In addition, propionate may inhibit gluconeogenesis by its metabolic conversion to methylmalonyl-CoA and succinyl-CoA. These metabolites could inhibit pyruvate carboxylase. Propionate may also reduce plasma levels of free fatty acids. High levels of free fatty acids lower glucose utilization and induce insulin resistance. Finally, propionate may enhance glycolysis via depletion of citrate in hepatocytes. Citrate is an allosteric inhibitor of phosphofructokinase.

Lactulose may bind/sequester such minerals as calcium and magnesium in the small intestine. The short-chain fatty acids formed from the bacterial fermentation of **lactulose** may facilitate the colonic absorption of calcium and, possibly, also magnesium ions. This could be beneficial in preventing osteoporosis and osteopenia.

PHARMACOKINETICS

Following ingestion, **lactulose** reaches the colon with very little digestion or absorption taking place in the stomach or small intestine. **Lactulose** is fermented by bifidobacteria, lactobacilli and some other bacteria in the colon to produce the short-chain fatty acids acetate, propionate and butyrate; the gases hydrogen, hydrogen sulfide, carbon dioxide and methane; and lactate, pyruvate, succinate and formate. Acetate, propionate and butyrate that are not metabolized in colonocyes are absorbed from the colon and transported via the portal circulation to the liver. These short-chain fatty acids are extensively metabolized in hepatocytes. Acetate, propionate and butyrate that are not metabolized in hepatocytes are transported by the circulation to various tissues, where they undergo further metabolism. Butyrate is an important respiratory fuel for the colonocytes. **Lactulose** is completely metabolized in the colon, and no **lactulose** is excreted in the feces.

Those with ileostomies may have a microbial flora colonizing their ileums. In those cases, **lactulose** could be fermented by some of the bacteria in a fashion similar to their fermentation in the colon.

INDICATIONS AND USAGE

Lactulose is used to treat **constipation** and hepatic encephalopathy. Preliminary research suggests that it might protect against a number of intestinal pathogens, that it might be helpful in the treatment of some inflammatory bowel diseases and that it could help prevent colorectal cancers. There is additional preliminary evidence suggesting that it could be of benefit in osteoporosis, diabetes mellitus and renal failure.

RESEARCH SUMMARY

Lactulose has proved effective in the treatment of some with chronic **constipation**, helping to restore normal peristalsis and defecation rhythm, softening stools and diminishing pain and other symptoms of dyspeptic disorders.

Lactulose is used with good results in some with compensated liver disease; **lactulose** has been shown in various studies to increase protein tolerance and help prevent hepatic encephalopathy.

Lactulose has helped protect against *Salmonella* infection and has shown activity against a number of other intestinal pathogens. It has reduced the incidence of bacterial translocation from the gut to mesenteric lymph nodes in rats with obstructive jaundice. It has also prevented bacterial translocation in animal models of surgical trauma. Other experiments suggest that **lactulose** might be helpful in idiopathic, as well as infectious inflammatory bowel diseases.

Lactulose has suppressed experimentally induced colonic aberrant crypt foci in rats and has helped protect colonic mucosa against a known colon carcinogen.

There is some early but promising clinical work. In one controlled study, patients who had undergone endoscopic removal of colorectal polyps were given antioxidant vitamins or **lactulose** to see if these substances could reduce the recurrence rate of adenomatous polyps. Over the course of this five-year study, polyps recurred in 5.7% of those taking the vitamins (A, C and E) and in 14.7% of those taking **lactulose**, compared with a recurrence rate of 35.9% in untreated controls. There were 209 subjects in the study.

Lactulose has also been shown to significantly stimulate calcium absorption in postmenopausal women, though the research has not yet been done to see whether it slows the rate of bone loss in aging subjects. There is, in addition, preliminary research suggesting that **lactulose** might improve glucose tolerance and have other effects on carbohydrate metabolism that could be of benefit in those with diabetes mellitus.

Finally, there is the suggestion in other preliminary research that **lactulose** might be helpful in the treatment of chronic renal failure. **Lactulose** has been shown to promote fecal excretion of water, sodium, potassium, amonium, urea, creatine and hydronium ions.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Some **lactulose** preparations contain galactose. Therefore, **lactulose** is contraindicated in those who require a low galactose diet. **Lactulose** is also contraindicated in those who are hypersensitive to any component of a **lactulose**-containing preparation.

PRECAUTIONS

In the United States, **lactulose** is a prescription drug. Its use requires medical supervision. Its use as a dietary supplement is considered experimental.

Those who develop gastrointestinal symptoms (flatus, bloating, diarrhea) with the use of dietary fiber should exercise caution in the use of **lactulose**.

Those with lactose intolerance should exercise caution in the use of **lactulose**.

One of the metabolites of **lactulose** is hydrogen gas. Hypothetically, this represents a potential hazard for those using **lactulose** who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of hydrogen gas in significant amounts in the presence of an electric spark may result in an explosion. Therefore, those undergoing these procedures should stop **lactulose** intake at least a week before the procedure.

Pregnant women and nursing mothers should avoid **lactulose**.

ADVERSE REACTIONS

Laxative doses are typically 20 to 40 grams daily. Doses up to 10 grams daily are usually well tolerated. Some may be more sensitive to the possible gastrointestinal side effects of **lactulose**. The adverse reactions are mainly gastrointestinal and include flatus and abdominal cramps. Doses of greater than 13 grams daily can cause diarrhea. Also, nausea and vomiting have been reported following the higher doses. Some find the taste of **lactulose** to be disagreeable.

INTERACTIONS

DRUGS

Concomitant use of nonabsorbable antacids with **lactulose** may inhibit the desired **lactulose**-induced drop in colonic pH which might affect laxative activity and activity in the treatment of hepatic encephalopathy.

NUTRITIONAL SUPPLEMENTS

The concomitant use of such probiotics as *Bifidobacterium longum* and **lactulose** may enhance the possible health benefits of **lactulose**.

Lactulose may enhance the colonic absorption of calcium and magnesium supplements if used concomitantly.

FOODS

Lactulose may enhance the colonic absorption of calcium and magnesium in foods.

OVERDOSAGE

There have been no reports of overdosage.

DOSAGE AND ADMINISTRATION

Lactulose is available in some functional foods and nutritional supplements in Japan. Its use in the U.S. for supplemental purposes is still experimental. Supplemental doses used in Japan are about 2 to 5 grams daily. Doses higher than 10 grams daily are likely to cause gastrointestinal side effects (flatus, abdominal cramping, diarrhea). Doses of 10 to 20 grams daily and up to 40 grams daily are used to treat **constipation**. Doses from 60 to 120 grams daily are used to treat hepatic encephalopathy. Pharmaceutical **lactulose** is available in solutions and in the form of a crystalline **powder**. **Lactulose** is a prescription drug in the U.S. for pharmaceutical uses.

HOW SUPPLIED

Powder — 10 g/packet

Solution — 10 g/15 ml

Syrup — 10 g/15 ml

LITERATURE

Bianchi G, Ronchi M, Marchesini G. Effects of **lactulose** on carbohydrate metabolism and diabetes mellitus. *Scand J Gastroenterol Suppl.* 1997; 222:62-64.

Challa A, Rao JR, Chawan CB, Shackelford L. *Bifidobacterium longum* and **lactulose** suppress azoxymethane-induced colonic aberrant crypt foci in rats. *Carcinogenesis.* 1997; 18:517-521.

Clausen MR, Mortensen PB. **Lactulose**, disaccharides and colonic flora. Clinical consequences. *Drugs.* 1997; 53:930-942.

Gardiner KR, Erwin PJ, Anderson NH, et al. **Lactulose** as an antiendotoxin in experimental colitis. *Br J Surg.* 1995; 82:469-472.

Horsmans Y, Solbreux PM, Daenens C, et al. **Lactulose** improves psychomotor testing in cirrhotic patients with subclinical encephalopathy. *Aliment Pharmacol Ther.* 1997; 11:165-170.

Huchzermeyer H, Schumann C. **Lactulose** -- a multifaceted substance. *Z Gastroenterol.* 1997; 35:945-955.

Ozcelik MF, Eroglu C, Pekmezci S, et al. The role of **lactulose** in the prevention of bacterial translocation in surgical trauma. *Acta Chir Belg.* 1996; 96:44-48.

Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics Company; 2000.

Ponz de Leon M, Roncucci L. Chemoprevention of colorectal tumors: role of **lactulose** and of other agents. *Scan J Gastroenterol Suppl.* 1997; 222:72-75.

Rowland IR, Bearne CA, Fischer R, Pool-Zobel BL. The effect of **lactulose** on DNA damage induced by DMH in the colon of human flora-associated rats. *Nutr Cancer.* 1996; 26:37-47.

Salminen S, Salminen E. **Lactulose**, lactic acid bacteria, intestinal microecology and mucosal protection. *Scand J Gastroenterol Suppl.* 1997; 222:45-48.

Teuri U, Vapaatalo H, Korpela R. Fructooligosaccharides and **lactulose** cause more symptoms in lactose maldigesters and subjects with pseudohypolactasia than in control lactose digesters. *Am J Clin Nutr.* 1999; 69:973-979.

Van den Heuvel EG, Muijs T, Van Dokkum W, Schaafsma G. **Lactulose** stimulates calcium absorption in postmenopausal women. *J Bone Miner Res.* 1999; 14:1211-1216.

PDR Drug information for

LACTULOSE

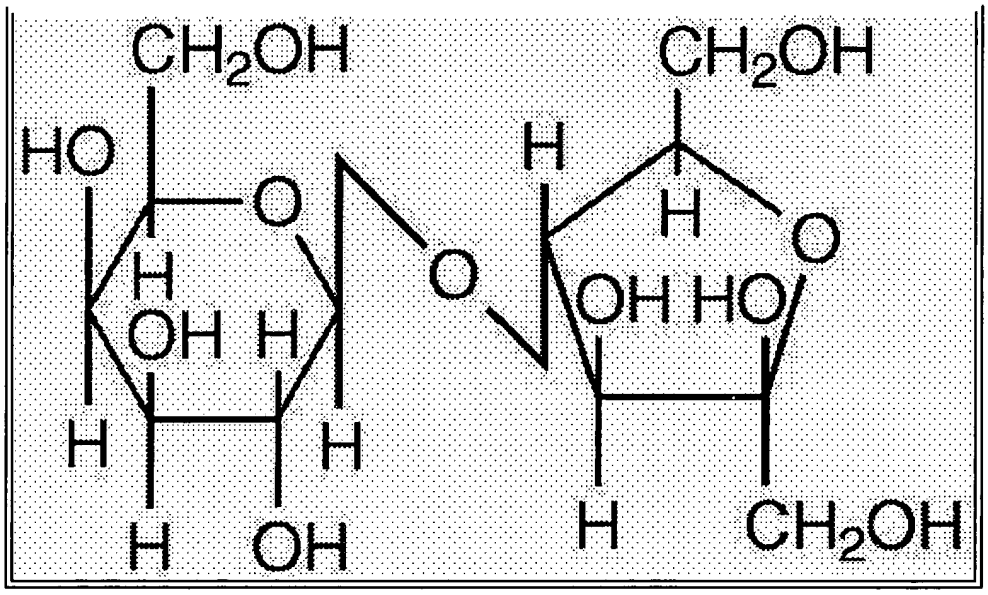
Manufacturer: Mylan Bertek

DESCRIPTION

KRISTALOSE™ (LACTULOSE) is a synthetic disaccharide in the form of crystals for reconstitution prior to use for oral administration. Each 10 g of lactulose contains less than 0.3 g galactose and lactose as a total sum. The pH range is 3.0 to 7.0

Lactulose is a colonic acidifier which promotes laxation.

The chemical name for lactulose is 4-O-(beta)-D-Galactopyranosyl-D-fructofuranose. It has the following structural formula:



The molecular formula is $C_{12}H_{22}O_{11}$. The molecular weight is 342.30. It is freely soluble in water.

CLINICAL PHARMACOLOGY

KRISTALOSE™ (LACTULOSE) is poorly absorbed from the gastrointestinal tract and no enzyme capable of hydrolysis of this disaccharide is present in human gastrointestinal tissue. As a result, oral doses of lactulose reach the colon virtually unchanged. In the colon, lactulose is broken down primarily to lactic acid, and also to small amounts of formic and acetic acids, by the action of colonic bacteria, which results in an increase in osmotic pressure and slight acidification of the colonic contents. This in turn causes an increase in stool water content and softens the stool.

Since lactulose does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce desired bowel movement.

Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

INDICATIONS AND USAGE

KRISTALOSE™ (LACTULOSE) For Oral Solution is indicated for the treatment of constipation. In patients with a history of chronic constipation, lactulose therapy increases the number of bowel movements per day and the number of days on which bowel movements occur.

CONTRAINDICATIONS

Since KRISTALOSE™ (LACTULOSE) For Oral Solution contains galactose (less than 0.3 g/10 g as a total sum with lactose), it is contraindicated in patients who require a low galactose diet.

WARNINGS

A theoretical hazard may exist for patients being treated with lactulose who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H_2 gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactulose, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with a non-fermentable solution. Insufflation of CO_2 as an additional safeguard may be

pursued but is considered to be a redundant measure.

PRECAUTIONS

General

Since KRISTALOSE™ (LACTULOSE) For Oral Solution contains galactose and lactose (less than 0.3 g/10 g as a total sum), it should be used with caution in diabetics.

Information for patients

In the event that an unusual diarrheal condition occurs, contact your physician.

Laboratory Tests

Elderly, debilitated patients who receive lactulose for more than six months should have serum electrolytes (potassium, chloride, carbon dioxide) measured periodically.

Drug Interactions

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility.

There are no known animal data on long-term potential for mutagenicity.

Administration of lactulose syrup in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

In studies in mice, rats, and rabbits, doses of lactulose syrup up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in mice, rats, and rabbits at doses up to 3 or 6 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Precise frequency data are not available.

Initial dosing may produce flatulence and intestinal cramps, which are usually transient. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia.

Nausea and vomiting have been reported.

OVERDOSAGE

Signs and Symptoms

There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

Oral LD_{50}

The acute oral LD_{50} of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis

Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

DOSAGE AND ADMINISTRATION

The usual adult dosage is 10 g to 20 g of lactulose daily. The dose may be increased to 40 g daily if necessary. Twenty-four to 48 hours may be required to produce a normal bowel movement.

DIRECTIONS FOR PREPARATION

Dissolve contents of packet in half a glass (4 ounces) of water.

When Lactulose for Oral Solution is dissolved in water, the resulting solution may be colorless to a slightly pale yellow color.

HOW SUPPLIED

KRISTALOSE™ (LACTULOSE) For Oral Solution is available in single dose packets of 10 g (NDC 62794-501-17) and single dose packets of 20 g (NDC 62794-502-17). The packets are supplied as follows:

NDC 62794-501-93 Carton of thirty 10 g packets

NDC 62794-502-93 Carton of thirty 20 g packets

STORE AT ROOM TEMPERATURE, 15°-30°C (59°-86°F).

Distributed by

BERTEK PHARMACEUTICALS INC.

Sugar Land, TX 77478

Manufactured by

Inalco S.p.A.

Milan, Italy

089.1

REVISED OCTOBER 2003

Vol. 36, No. 3, 2004

Free Abstract Article (References) Article (PDF 68 KB)

Original Paper

Effects of Hyperosmolar Agents - Lactulose, Lactitol, Sodium Phosphate and Polyethylene Glycol - on Cecal Coliform Bacteria during Traditional Bowel Cleansing: An Experimental Study in Rats

B. Demirogullari[a], A. Poyraz[b], M.Y. Cirak[c], K. Sonmez[a], I.O. Ozen[a], C. Kulah[b], B. Karabulut[a], A.C. Basaklar[a], N. Kale[a]

Departments of
[a]Pediatric Surgery,
[b]Pathology and
[c]Microbiology, Gazi University Faculty of Medicine, Ankara, Turkey

Address of Corresponding Author

European Surgical Research 2004;36:159-164 (DOI: 10.1159/000077258)

Key Words

- Bowel cleansing
- Lactulose
- Lactitol
- Polyethylene glycol
- Sodium phosphate
- Bacterial translocation

Abstract

Mechanical bowel cleansing is considered to be necessary prior to colorectal surgery, some radiological or endoscopic procedures, and for fecal disimpaction. Traditional bowel cleansing (TBC) with cathartics and enemas is a method of mechanical bowel cleansing for patients who have restrictive factors for whole-bowel irrigation (WBI), such as excessive fecal impaction, cardiac, hepatic or renal disorders. In this experimental study, TBC with hyperosmolar agents was evaluated in terms of their effects on colonic flora and bacterial translocation (BT). Sprague-Dawley rats were divided into 6 groups. The animals, except controls, were not fed for 72 h but received tap water ad libitum. During this period, lactulose, lactitol, sodium phosphate (NaP), polyethylene glycol 3350 (PEG3350) and physiological

saline gavages were administered to the rats in groups 1-5, respectively, once a day. All animals except controls (group 6) received enemas with 15 ml of warm saline twice a day. The cecum, mesenteric lymph nodes (MLNs) and portal vein blood were sampled for microbiological and histopathological analysis. The highest level of coliform bacterial overgrowth and BT to MLNs were observed in the lactulose group, although the others, except the saline and control groups, also caused some degree of BT. Portal vein cultures were negative for all groups. Histopathological damage was not associated with cecal bacterial count and BT. As a result of this study, PEG3350 seems to be safer and more effective than lactulose, lactitol and NaP during TBC.

Author Contacts

Billur Demirogullari
Cigdem Mh, Ebru 2 Sitesi, F Blok, No:34
TR-06530 Balgat, Ankara (Turkey)
Tel. +90 312 285 95 50, Fax +90 312 212 99 08
E-Mail billurd@yahoo.com

Article Information

Received: July 26, 2003
Accepted after revision: December 12, 2003
Number of Print Pages : **6**
Number of Figures : **0**, Number of Tables : **2**, Number of References : **45**

Free Abstract Article (References) Article (PDF 68 KB)